Lead Optimization of Novel Boron-Containing Drug Candidates for the Treatment of Human African Trypanosomiasis

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Abstract

Human African Trypanosomiasis (HAT) represents a significant public health problem in sub-Saharan Africa affecting hundreds of thousands of individuals. An urgent need exists for the discovery and development of new, safe, and effective drugs to treat HAT, as existing therapies suffer from poor safety profiles, difficult treatment regimens, limited effectiveness, and a high cost of goods. From a collaborative effort between SCYNEXIS, Anacor Pharmaceuticals, Pace University, and DNDi, we report ongoing lead optimization efforts on a novel class of small molecule boron-containing compounds, exemplified by SCYX-6759. These compounds inhibit T. brucei growth in vitro with good PK and physiochemical properties. Functionalization of the C-3 position on the oxaborole ring has significantly improved overall PK properties, particularly by increasing CNS disposition and retention.

Oxaborole 6-N-Benzamides

- Active against T. brucei in vivo, with good PK and physiochemical properties.
- Efficacious in vivo against both acute (Stage I) and CNS (Stage II) infection in mouse model.
- Exemplified by SCYX-6759

Acute In Vivo Efficacy (Stage I)

- Series demonstrates robust in vivo activity in mouse model.
- *Cure = No parasitemia detectable for >30 days
- **Also fully efficacious at 5 mg/kg, p.o., b.i.d. (3/3 cured)

In Vivo Pharmacokinetics

- SCYX-7158 sustains >MIC in CNS for over 24 hours
- Excellent PK and CNS disposition at small cost to potency

Functionalization of the C-3 position on the oxaborole ring has significantly improved overall PK properties, particularly by increasing CNS disposition and retention.

The optimized lead compound (SCYX-7158) is currently demonstrating robust in vivo activity against stage II trypanosomiasis at clinically relevant dosing levels in ongoing studies.

Further biological, toxicological and pharmacokinetic profiling of SCYX-7158 is also in progress.

Summary

- Oxaboroles have been identified as a promising lead series for the treatment of HAT; demonstrating high in vitro potency vs. T. brucei and good PK and physiochemical properties.
- Lead optimization of the 6-N benzamide region has afforded compounds that are orally active in murine models of both acute (stage I) and chronic (stage II) trypanosomiasis.
- The optimized lead compound (SCYX-7158) is currently demonstrating robust in vivo activity against stage II trypanosomiasis at clinically relevant dosing levels in ongoing studies.
- Further biological, toxicological and pharmacokinetic profiling of SCYX-7158 is also in progress.